

Remarks

This Amendment is being filed concurrently with a Request for Continued Examination. In order to advance prosecution of the Application, presented below are arguments in response to the rejections made in the final Office Action mailed on July 23, 2009.

After entry of this Amendment, claims 106, 112-115, 118, 120, 121, 123, 124, 129-136, and 138, as amended, will be pending for the Examiner's review and consideration. Claims 107-111, 116, 117, 119, 122, 125-128, and 137 have been canceled without prejudice. The right to prosecute the subject matter of any or all of the canceled claims in this or in a subsequent continuation, continuation-in-part, or divisional application is hereby expressly reserved.

Claim Amendments:

Claims 106 and 124 have been amended to incorporate the subject matter of former claims 122 and 137, respectively, and recite that the vesicle has a size of 75 to 400 nm. This amendment is supported, for example, on page 10, lines 1 to 3 of the Specification as filed.

Claim 124 has been amended to delete the language "an aqueous medium."

No new matter has been added to the claims by these amendments.

Claim Rejections – 35 U.S.C. § 112, first paragraph:

Claims 106, 112-115, 118, 120-124, and 129-138 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The Office asserts that the specification does not describe a vesicle "consisting essentially of" a phosphatidylcholine and a salt of an NSAID. This rejection has been rendered moot as to claims 122 and 137 by their cancellation without prejudice. As to claims 106, 112-115, 118, 120, 121, 123, 124, 129-136, and 138, the rejection is respectfully traversed for the reasons set forth below.

In response, the Office's attention is invited to the as-filed application at page 18, lines 9-12 and 16-26, and page 19, lines 1-4, which are believed to disclose the vesicles recited in the claims.

Page 18, lines 9-12 and 16-26 state, respectively (emphases added):

Preferably, the active ingredient is a non-steroidal anti-inflammatory drug, such as diclofenac, ibuprofen or a lithium, sodium, potassium, cesium, rubidium, ammonium, monomethyl, dimethyl, trimethylammonium or ethylammonium salt thereof.

As less polar components, inventive preparations may contain a physiologically compatible lipid, preferably from the class of phospholipids and especially from the class of phosphatidyl cholines, the active ingredient, for example, ibuprofen, diclofenac or a salt thereof, being the more soluble component, optionally with the addition of less than 10% by weight, based on the total composition of the preparation of a further soluble component and the concentration of the more soluble component(s) typically being between 0.01% by weight and 15% by weight, preferably between 0.1% and 10% by weight and particularly between 0.5% by weight and 3% by weight, and the total lipid concentration being between 0.005% by weight and 40% by weight and preferably between 0.5% by weight and 15% by weight and especially between 1% by weight and 10% by weight.

Page 19, lines 1-4, states:

Inventive preparations additionally may comprise consistency modifiers, such as hydrogels, antioxidants such as probucol, tocopherol, BHT, ascorbic acid, desferroxamine and/or stabilizers such as phenol, cresol, benzyl alcohol, etc.

For these reasons, it is believed that the claims find written description support in the specification as filed, and that this ground of rejection should be withdrawn.

Claim Rejections – 35 U.S.C. § 112, second paragraph:

Claims 124 and 129-138 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite by virtue of the misplaced term “an aqueous medium.” This rejection has been rendered moot as to claim 137 by its cancellation without prejudice. Further, claims 124, 129-136, and 138 have been amended to delete the language “an aqueous medium.” Accordingly, this ground of rejection has been overcome and should be withdrawn.

Claim Rejections – 35 U.S.C. § 103(a):

Claims 106, 112-115, 118, 120-124, and 129-138 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Vyas, et al., *J. Microencapsulation*, 1995, 12(2), 149-154 (“Vyas”); U.S. patent No. 5,585,109 to Hayward, et al. (“Hayward”); or U.S. patent No. 4,937,254 to Sheffield, et al. (“Sheffield”) in combination with U.S. patent No. 5,043,165 to Radhakrishnan (“Radhakrishnan”) or U.S. patent No. 5,498,420 to Edgar, et al. (“Edgar”), by themselves or together in further combination with U.S. patent No. 4,897,269 to Mezei (“Mezei”). This rejection has been rendered moot as to claims 122 and 137 by their cancellation without prejudice. As to claims 106, 112-115, 118, 120, 121, 123, 124, 129-136, and 138, the rejection is respectfully traversed for the reasons set forth below.

“the vesicle has a size of 75 to 400 nm”

None of the primary references Vyas, Hayward, or Sheffield suggests, much less discloses, the recited vesicles having a size of 75 nm to 400 nm.

Vyas refers to vesicles having an average size of about 3820 nm to about 5090 nm (Vyas, Table 1), Sheffield refers to vesicles having a size of about 1000 nm to about 5000 nm (Sheffield, col. 6, ll. 33-34), and Hayward is silent as to vesicle size. The vesicles of Vyas and Sheffield are at least 13 times larger than the vesicles recited in the present claims.

None of Vyas, Hayward, or Sheffield suggests reducing the vesicle size at all, much less by the substantial amount required to achieve the vesicle size of 75 nm to 400 nm recited in the present claims. In fact, Sheffield stresses the importance of using

vesicles of “comparatively large size” in order to aid in treatment of a patient: “The use of MLV’s of comparatively large size (e.g., from about 1 to about 5 microns) appears to be preferable in order to increase the dwell time of the vesicle containing the NSAID in the peritoneal cavity (or other body cavity).” (Sheffield, col. 6, ll. 33-37). Thus, Sheffield teaches away from the use of vesicles of smaller size. A reference that teaches away can defeat a finding of obviousness. *Winner Int’l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-1350 (Fed. Cir. 2000).

The secondary reference Edgar further teaches away from the use of the 75 nm to 400 nm vesicles recited in the claims by cautioning that contrary to liposomes that are smaller than 30 nm, “large liposomes having a size of over 60 nm get caught in the upper skin layers where they release the active substance.” (Edgar, col. 3, ll. 5-7).

“a salt of one or more non-steroidal anti-inflammatory drugs”

None of the primary references references Vyas, Hayward, or Sheffield discloses or suggests the recited vesicles having a salt of one or more NSAIDs.

The Office states that Hayward discloses vesicles having a salicylate salt (an NSAID salt) based on Hayward’s disclosure of the preparation of a vesicle having salicylic acid and whose pH is adjusted to 6.5 to 7.5. The Office contends, without any scientific evidence whatsoever, that the salicylic acid in the Hayward vesicle, therefore, must be in the form of a salicylate salt. However, when the passage of Hayward on which the Office relies is read in its full context, it makes clear that less than 1% of the salicylic acid is converted to a salicylate salt:

The composition of the present invention may be prepared by the following process steps, which are carried out at room temperature (25C) under 1 atmosphere pressure of argon gas (to limit any opportunity for oxidation):

* * *

d) The pH of the batch at this stage is acidic (pH approximately 2.0) due to the limited solubility of salicylic acid in water (approximately 0.2%). A batch titration was then performed with arginine to achieve a final pH of 6.5 to 7.5. The amount of arginine required is determined by the

total availability of titratable groups. However, less than 1% salicylic acid is neutralized by this process.

(Hayward, col. 5, ll. 10-13 and 44-52, emphasis added). Accordingly, Hayward clearly teaches away from the vesicles of the presently claimed invention.

Further, as previously argued, Hayward repeatedly teaches away from the use of salicylate salts, for example, as follows:

- “More particularly, the present invention relates to a cosmetic dispersion that allows for the incorporation of large amounts of salicylic acid within the hydrophobic compartment of the liposomal bilayer, without the necessity of pre-neutralization or salt formation of the corresponding salicylate . . .” *Id.* at col. 1, ll. 15-20 (emphasis added).
- “The advantages of the [Hayward] invention include the fact that the cosmetic composition has the unexpected ability to sustain a neutral pH (7.0) in the external aqueous milieu, without neutralizing the salicylic acid to the corresponding salicylate.” *Id.* at col. 4, ll. 27-31 (emphasis added).
- “The formation of salts of salicylic acid, such as sodium salicylate formed by the combination of salicylic acid and sodium hydroxide, greatly improves the water solubility of the free acid, but substantially modifies the biological response to salicylic acid.” *Id.* at col. 1, ll. 30-34 (emphasis added).

The secondary references Radhakrishnan, Edgar, and Mezei cannot remedy the above-described deficiencies of Hayward because they too fail to disclose or suggest the recited vesicles having a salt of one or more NSAIDs.

Radhakrishnan and Mezei are further distinguishable from the present claims in that they each emphasize the importance of including cholesterol in the vesicles. For example, all of the working examples of Mezei refer to vesicles that have both phosphatidyl choline and cholesterol. (Mezei, col. 7, l. 59 to col. 20, l. 20 (examples 1 to 11)). And Radhakrishnan states that “[t]he cholesterol sulfate and cholesterol are mandatory components of the nonconventional liposome formation and are not interchangeable with a phospholipids [sic], normally used in conventional liposome

compositions.” (Radhakrishnan, col. 14, ll. 41-45). The transitional phrase “consisting essentially of,” as it relates to the vesicles of the present claims, excludes cholesterol from the vesicles.

Because none of the primary references Vyas, Hayward, or Sheffield, either alone or in combination with Radhakrishnan or Edgar by themselves or in further combination with Mezei discloses or suggests all of the recitations of present claims 106, 112-115, 118, 120, 121, 123, 124, 129-136, and 138, it is believed that the Office has failed to make out a *prima facie* case of obviousness of these claims. Accordingly, the rejections of these claims under 35 U.S.C. § 103(a) as obvious over Vyas, Hayward, or Sheffield in view of Radhakrishnan or Edgar, by themselves or in further combination with Mezei cannot stand and should be withdrawn by the Office.

Conclusion:

In view of the foregoing amendments and remarks, it is respectfully submitted that the claims are in condition for allowance. Early and favorable action by the Examiner is earnestly solicited. If any outstanding issues remain, the Examiner is invited to contact the undersigned at (212) 497-7731 to discuss the same.

No fee is believed to be due for the submission of this response. Should any fees be required, please charge all such fees to Wilson, Sonsini, Goodrich & Rosati Deposit Account No. 23-2415 (Docket No. 35946-701.831).

Respectfully submitted,

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